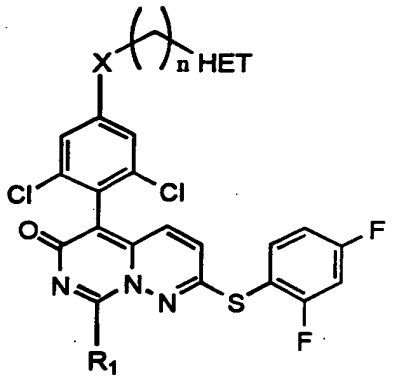
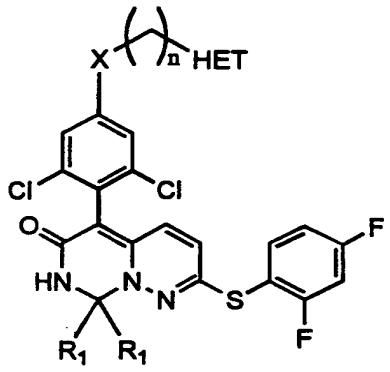
CLAIMS

We claim:

1. A compound having the formula:



I or



II,

or tautomers thereof or pharmaceutically acceptable salts thereof; wherein:

HET is a 5-7-membered heterocycle with 1 to 4 N, S or O atoms, which heterocycle is substituted with 1 to 3 C_1-C_4 branched or straight chain alkyl groups. HET may optionally be substituted with halo, cyano, $N(R')_2$, OR', CO_2R', $CON(R')_2$, and $SO_2N(R^2)_2$;

X is O or NR';

n is 1 to 3;

R' is selected from hydrogen, (C_1-C_3)-alkyl, (C_2-C_3)-alkenyl or alkynyl, phenyl or phenyl substituted with 1 to 3 substituents independently selected from halo, methoxy, cyano, nitro, amino, hydroxy, methyl or ethyl; or a 5-6 membered heterocyclic ring system optionally substituted with 1 to 3 substituents independently selected from halo, methoxy, cyano, nitro, amino, hydroxy, methyl or ethyl;

R_1 is selected from hydrogen, (C_1-C_3)-alkyl, OH, or O-(C_1-C_3)-alkyl;

R^2 is selected from hydrogen, (C_1-C_3)-alkyl, or (C_1-C_3)-alkenyl; each optionally substituted with $-N(R')_2$, $-OR'$, SR', $-C(O)-N(R')_2$, $-S(O_2)-N(R')_2$, $-C(O)-OR'$, or R^3; and

R^3 is selected from 5-6 membered aromatic carbocyclic or heterocyclic ring systems.

2. The compound according to claim 1, wherein R_1 is hydrogen.

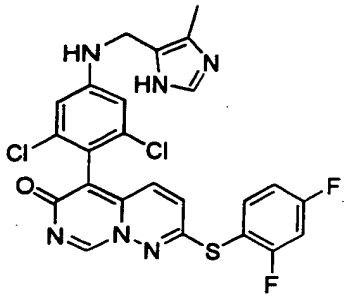
3. The compound according to claim 1, wherein n is 1.

4. The compound according to claim 1, wherein HET is an imidazole, triazole, thiazole, oxazole, pyridyl or pyrimidyl ring substituted with 1 to 3 C_1-C_4 branched or straight chain alkyl groups.

5. The compound according to claim 1, wherein R_1 is hydrogen, n is 1, and HET is an imidazole, triazole, thiazole, oxazole, pyridyl or pyrimidyl ring substituted with 1 to 3 C_1-C_4 branched or straight chain alkyl groups.

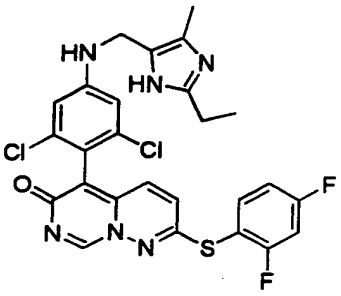
6. The compound according to claim 5, wherein R_1 is H, n is 1 and HET is an imidazole or pyridyl ring substituted with a C_1-C_3 alkyl group.

7. The compound according to claim 1, wherein said compound is



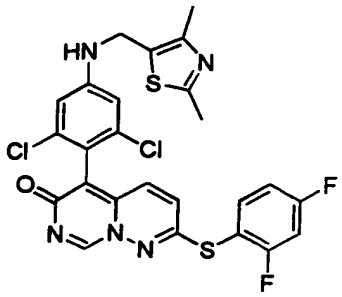
Compound 11.

8. The compound according to claim 1, wherein said compound is



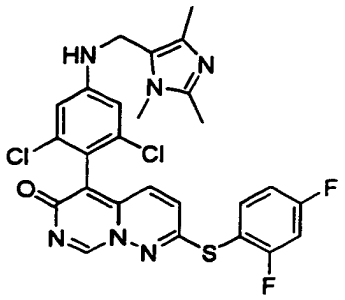
Compound 12.

9. The compound according to claim 1, wherein said compound is



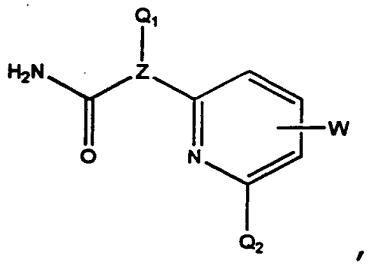
Compound 13.

10. The compound according to claim 1, wherein said compound is



Compound 14.

11. A compound having the formula:



, or tautomers thereof or pharmaceutically acceptable salts thereof, wherein:

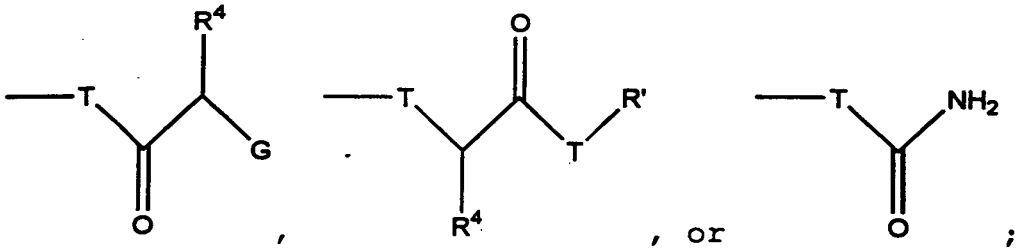
each of Q_1 and Q_2 are independently selected from 5-6 membered aromatic carbocyclic or heterocyclic ring systems, or 8-10 membered bicyclic ring systems comprising aromatic carbocyclic rings, aromatic heterocyclic rings or a combination of an aromatic carbocyclic ring and an aromatic heterocyclic ring; wherein

the rings that make up Q_1 are optionally substituted with 1 to 4 substituents, each of which is independently selected from J; halo; C_1-C_4 alkyl optionally substituted with NR'_2, OR', CO_2R' or $CONR'_2$; O-(C_1-C_4)-alkyl optionally substituted with A, T-C(O)R', OPO_3H_2, NR'_2, NR'_2, OR', CO_2R' or $CONR'_2$; NR'_2; OCF_3; CF_3; NO_2; CO_2R'; CONR'; SR'; $S(O_2)N(R')_2$; SCF_3; CN; $N(R')C(O)R^4$; $N(R')C(O)OR^4$; $N(R')C(O)C(O)R^4$; $N(R')S(O_2)R^4$; $N(R')R^4$; $N(R^4)_2$; OR^4; $OC(O)R^4$; $OP(O)_3H_2$; or $N=C-N(R')_2$; and wherein

the rings that make up Q_2 are substituted with J and optionally substituted with halo, C_1-C_4 straight chain or branched alkyl, hydroxy, methoxy, trifluoromethyl, trifluoromethoxy, cyano, or amino;

J is a C_1-C_4 straight chain or branched alkyl derivative substituted with 1-3 substituents selected from A, -T-C(O)R′ or $-OPO_3H_2$;

A is selected from the groups:



;

T is either O or NH;

G is either NH_2 or OH;

Z is either CH or N;

R′ is selected from hydrogen, $(C_1$-$C_3)$-alkyl, $(C_2$-$C_3)$-alkenyl or alkynyl, phenyl or phenyl substituted with 1 to 3 substituents independently selected from halo, methoxy, cyano, nitro, amino, hydroxy, methyl or ethyl; or a 5-6 membered heterocyclic ring system optionally substituted with 1 to 3 substituents independently selected from halo, methoxy, cyano, nitro, amino, hydroxy, methyl or ethyl;

R^3 is selected from 5-6 membered aromatic carbocyclic or heterocyclic ring systems;

R^4 is $(C_1$-$C_4)$-alkyl optionally substituted with $N(R')_2$, OR′, CO_2R', $CON(R')_2$, or $SO_2N(R^2)_2$; a 5-6 membered carbocyclic or heterocyclic ring system optionally substituted with a $(C_1$-$C_4)$ branched or straight-chain

alkyl group, $N(R')_2$, OR', CO_2R', $CON(R')_2$, or $SO_2N(R^2)_2$; or a (C_1-C_4)-alkyl optionally substituted with the 5-6 membered carbocyclic or heterocyclic ring system optionally substituted with a (C_1-C_4) branched or straight-chain alkyl group, $N(R')_2$, OR', CO_2R', $CON(R')_2$, or $SO_2N(R^2)_2$;

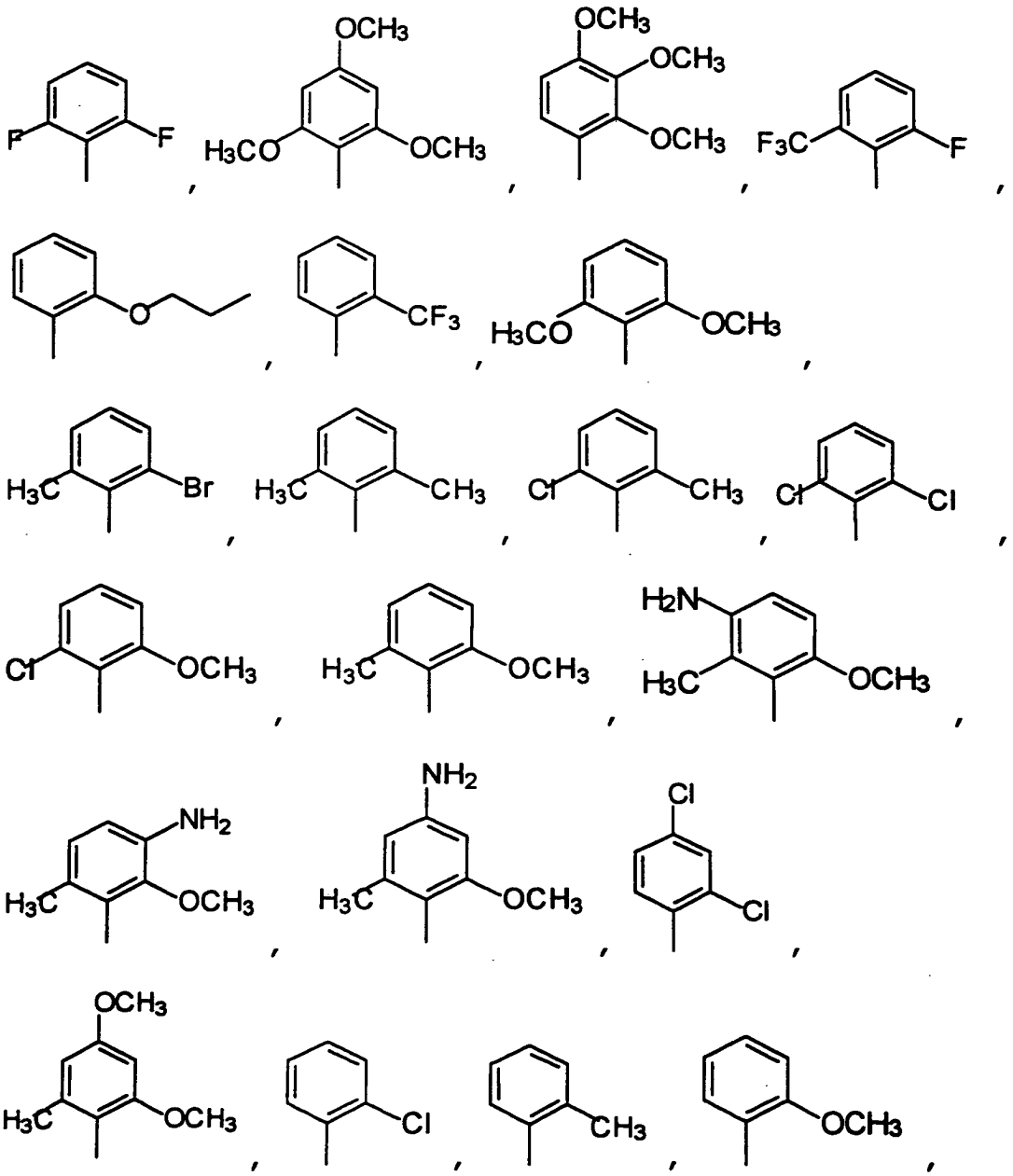
R^2 is selected from hydrogen, (C_1-C_3)-alkyl, or (C_1-C_3)-alkenyl; each optionally substituted with $-N(R')_2$, $-OR'$, SR', $-C(O)-N(R')_2$, $-S(O_2)-N(R')_2$, $-C(O)-OR'$, or R^3; and

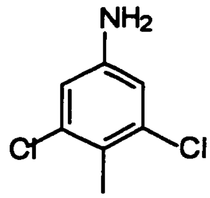
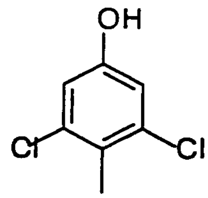
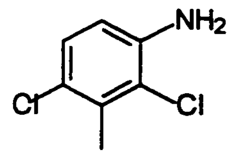
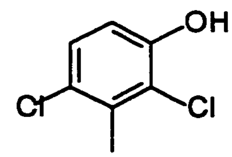
W is selected from H; $N(R^2)SO_2-N(R^2)_2$; $N(R^2)SO_2-N(R^2)(R^3)$; $N(R^2)C(O)-OR^2$; $N(R^2)C(O)-N(R^2)_2$; $N(R^2)C(O)-N(R^2)(R^3)$; $N(R^2)C(O)-R^2$; $N(R^2)_2$; $C(O)-R^2$; $CH(OH)-R^2$; $C(O)-N(R^2)_2$; $C(O)-OR^2$; or (C_1-C_4) straight or branched alkyl optionally substituted with A, $T-(CO)R'$, $N(R')_2$, OR', CO_2R', $CON(R')_2$, R^3, or $SO_2N(R^2)_2$; or a 5-6 membered carbocyclic or heterocyclic ring system optionally substituted with $N(R')_2$, OR', CO_2R', $CON(R')_2$, or $SO_2N(R^2)_2$.

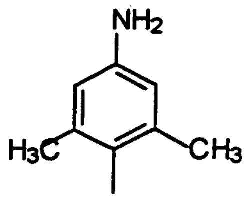
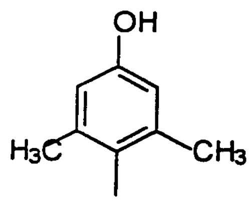
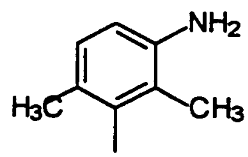
12. The compound according to claim 11, wherein Q_1 is selected from phenyl or pyridyl containing 1 to 3 substituents independently selected from chloro, fluoro, bromo, $-CH_3$, $-OCH_3$, $-OH$, $-CF_3$, $-OCF_3$, $-O(CH_2)_2CH_3$, NH_2, 3,4-methylenedioxy, $-N(CH_3)_2$, $-NH-S(O)_2$-phenyl, $-NH-C(O)O-CH_2$-4-pyridine, $-NH-C(O)CH_2$-morpholine, $-NH-C(O)CH_2-N(CH_3)_2$, $-NH-C(O)CH_2$-piperazine, $-NH-C(O)CH_2$-pyrrolidine, $-NH-C(O)C(O)$-morpholine, $-NH-C(O)C(O)$-piperazine, $-NH-C(O)C(O)$-pyrrolidine, $-O-C(O)CH_2-N(CH_3)_2$, or $-O-(CH_2)_2-N(CH_3)_2$ and wherein at least one of said substituents is in the ortho position.

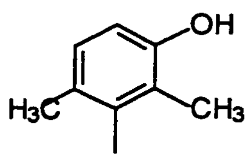
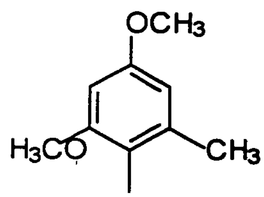
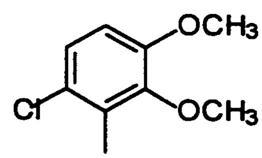
13. The compound according to claim 12, wherein Q_1 contains at least two substituents, both of which are in the ortho position.

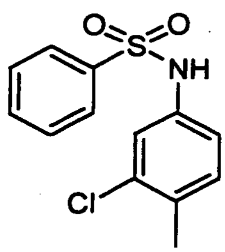
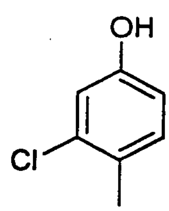
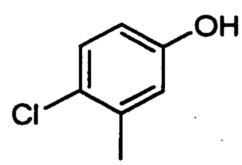
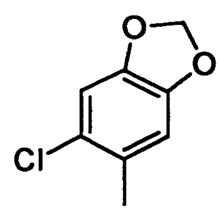
14. The compound according to claim 12, wherein Q_1 is selected from:

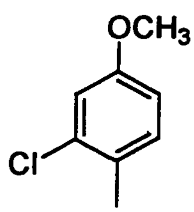
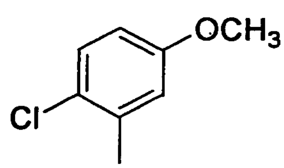
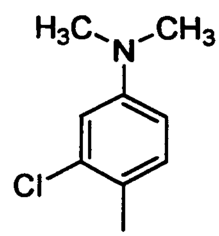
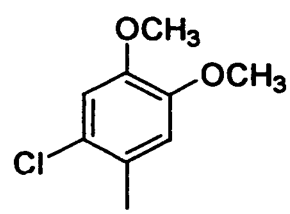


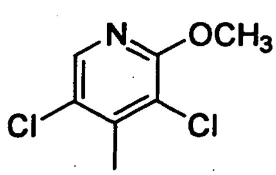
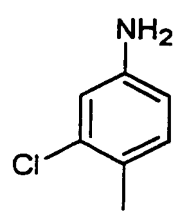
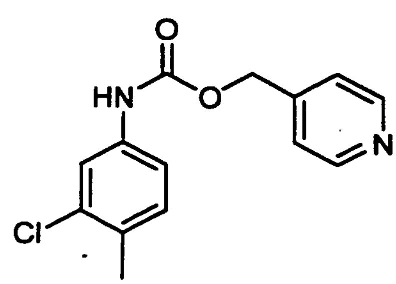
 ,  ,  ,  ,

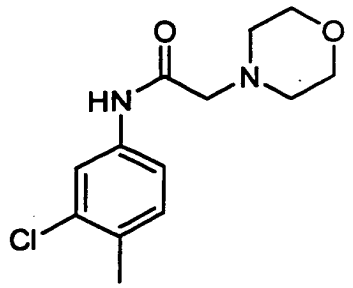
 ,  ,  ,

 ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,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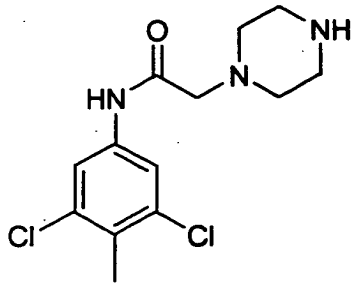
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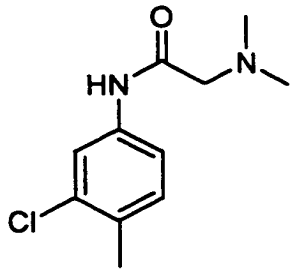
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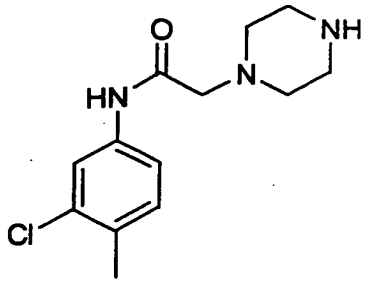
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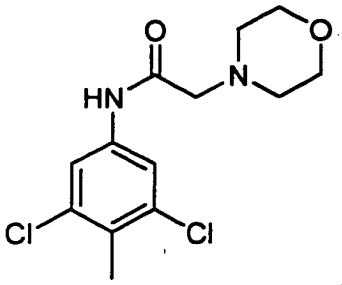
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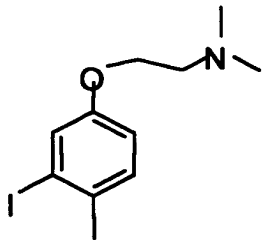
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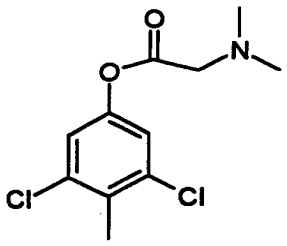
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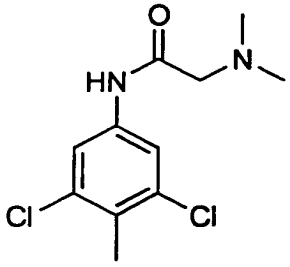
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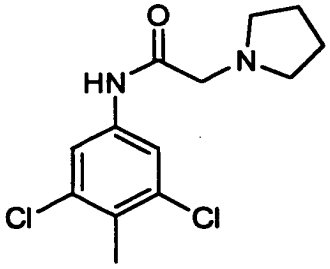
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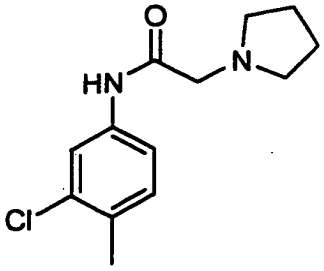
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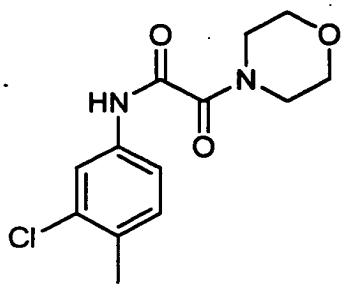
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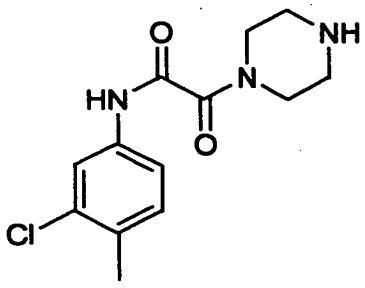
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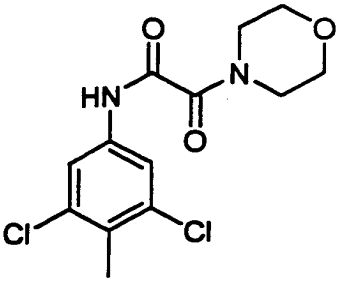
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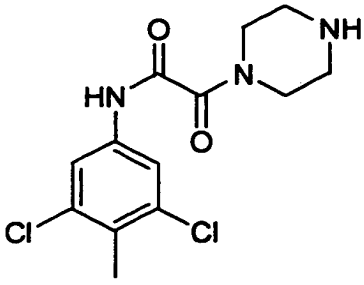
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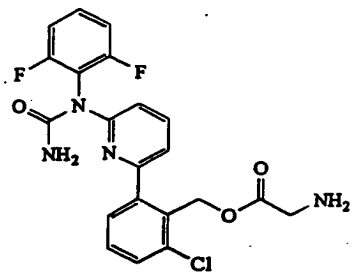
15. The compound according to claim 14, wherein Q_1 is selected from 2-fluoro-6-trifluoromethylphenyl; 2,6-difluorophenyl; 2,6-dichlorophenyl; 2-chloro-4-hydroxyphenyl; 2-chloro-4-aminophenyl; 2,6-dichloro-4-aminophenyl; 2,6-dichloro-3-aminophenyl; 2,6-dimethyl-4-hydroxyphenyl; 2-methoxy-3,5-dichloro-4-pyridyl; 2-chloro-4,5 methylenedioxy phenyl or 2-chloro-4-(N-2-morpholino-acetamido)phenyl.

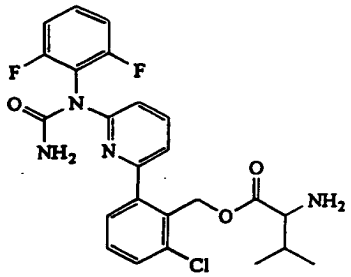
16. The compound according to claim 11 wherein Q_2 is selected from phenyl or pyridyl, said phenyl or said pyridyl containing the substituent J and 0 to 3 other substituents, wherein each of said other substituents is independently selected from chloro, fluoro, bromo, methyl, ethyl, isopropyl, $-OCH_3$, $-OH$, $-NH_2$, $-CF_3$, $-OCF_3$, $-SCH_3$, $-OCH_3$, $-C(O)OH$, $-C(O)OCH_3$, $-CH_2NH_2$, $-N(CH_3)_2$, $-CH_2$-pyrrolidine and $-CH_2OH$.

17. The compound according to claim 11, wherein said compound is



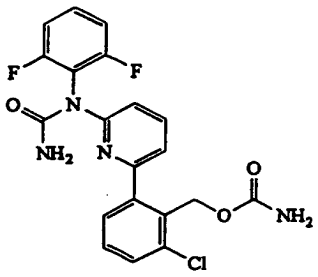
Compound 15.

18. The compound according to claim 11, wherein said compound is



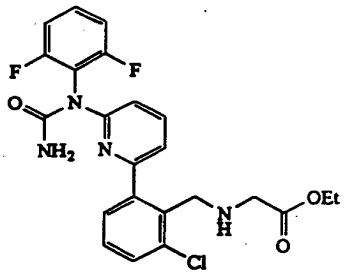
Compound 16.

19. The compound according to claim 11, wherein said compound is



Compound 17.

20. The compound according to claim 11, wherein said compound is



Compound 18.

21. A composition comprising a compound according to either claim 1 or claim 11 and a pharmaceutically acceptable carrier.

22. A method of treating or preventing inflammatory diseases, autoimmune diseases, destructive

bone disorders, proliferative disorders, infectious diseases, neurodegenerative diseases, allergies, reperfusion/ischemia in stroke, heart attacks, angiogenic disorders, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin-induced platelet aggregation or conditions associated with prostaglandin endoperoxidase synthase-2 in a patient, said method comprising administering to said patient a composition according to claim 21 in an amount effective to inhibit p38.

23. The method according to claim 22, wherein said method is used to treat or prevent an inflammatory disease selected from acute pancreatitis, chronic pancreatitis, asthma, allergies, or adult respiratory distress syndrome.

24. The method according to claim 22, wherein said method is used to treat or prevent an autoimmune disease selected from glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, or graft vs. host disease.

25. The method according to claim 22, wherein said method is used to treat or prevent a destructive bone disorders selected from osteoarthritis, osteoporosis or multiple myeloma-related bone disorder.

26. The method according to claim 22, wherein said method is used to treat or prevent a proliferative disease selected from acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, or multiple myeloma.

27. The method according to claim 22, wherein said method is used to treat or prevent an infectious disease selected from sepsis, septic shock, or Shigellosis.

28. The method according to claim 22, wherein said method is used to treat or prevent a viral disease selected from acute hepatitis infection, HIV infection or CMV retinitis.

29. The method according to claim 22, wherein said method is used to treat or prevent a neurodegenerative disease selected from Alzheimer's disease, Parkinson's disease, cerebral ischemia or neurodegenerative disease caused by traumatic injury.

30. The method according to claim 22, wherein said method is used to treat or prevent ischemia/reperfusion in stroke or myocardial ischemia, renal ischemia, heart attacks, organ hypoxia or thrombin-induced platelet aggregation.

31. The method according to claim 22, wherein said method is used to treat or prevent a condition

associated with prostaglandin endoperoxide synthase-2 selected from edema, fever, analgesia or pain.

32. The method according to claim 31, wherein said pain is selected from neuromuscular pain, headache, cancer pain, dental pain or arthritis pain.

33. The method according to claim 22, wherein said method is used to treat or prevent an angiogenic disorder selected from solid tumors, ocular neovasculization, or infantile haemangiomas.